Interpretation of erythropoietin levels in patients with various degrees of renal anemia

To the Editor: In interesting paper, Fehr et al [1] showed relative erythropoietin deficiency in patients with GFR <40 mL/min, and concluded that it was the sequence of either altered set point for hormone production or due to renal tissue damage. On the other hand, Machiguchi et al's paper [2] and our preliminary study led to extend Fehr's explanation. Machiguchi et al [2] have shown that in patients with IgA nephropathy and relatively preserved renal function (sCr 0.5-2.5 mg/dL), urinary excretion of N-acetyl-β-D-glucosaminidase (NAG) inversely correlated with serum erythropoietin concentration. According to these results, our recent study by Sulikowska et al [3] showed that functional status of renal vasculature, estimated as dopamine-induced glomerular filtration response (DIR), strongly correlated with NAG excretion. Furthermore, our preliminary study conducted in 30 untreated IgA patients, with GFR 109 ± 27.5 mL/min, showed that DIR correlated with changes of serum erythropoietin concentration during dopamine infusion (serum erythropoietin, before dopamine mean: 10.9, range: from 1.3 to 10.4; after dopamine mean: 9.2, range: from 1.8 to 29.1 U/L) and 24-hour proteinuria ($r = -48$; $P < 0.05$), ($r = 37$; $P < 0.05$), respectively. In the same study, dopamine-induced changes of serum erythropoietin correlated with both 24-hour urinary NAG excretion and proteinuria ($r = 0.56$; $P < 0.02$), ($r = 0.43$; $P < 0.03$), respectively. Data from Machiguchi et al [2], together with our finding, suggest that proteinuria is a crucial factor disturbing the function of tubulointerstitial compartment (tubules, vessels, and interstitial cells) as a whole. Presented data, and comments of Fehr et al, suggest that serum erythropoietin concentration come into view as a marker of functional status of tubulointerstitial compartment in patients with various degrees of renal damage. Regarding these data, we have commenced the study to examine whether serum erythropoietin could be used as a marker to predict the progression of renal disease.

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Reply from the Authors

We would like to thank Sulikowska et al for their comments to our study [1]. We were not aware of the cited study performed in patients with IgA nephropathy and moderate renal insufficiency, which showed that urinary N-acetyl-β-D-glucosaminidase (NAG) excretion inversely correlated with serum erythropoietin levels [2]. Together with their own data also obtained in patients with IgA nephropathy, the authors suggest that serum erythropoietin may be a marker for the functional status of the tubulointerstitial compartment in patients with various degrees of renal damage.

Although this hypothesis is intriguing and worth to pursue further, there are "caveats." First, NAG is commonly used as a marker for tubular damage. Sulikowska et al mention that NAG excretion in their patients positively correlated with proteinuria, and that the latter may be responsible for tubular dysfunction, as described earlier [3]. However, in order to prove the tubular origin of NAG, they should formally exclude the possibility of glomerular filtration of NAG in the context of nonselective glomerular proteinuria. They would have to demonstrate the absence of immunoglobulins in the urine, which have about the same molecular weight as NAG, and measure other tubular markers (as α1-microglobulin).

Second, the findings in patients with IgA nephropathy may not be generalizable for all patients with renal insufficiency. The same is true for our own findings, which were obtained in a population with mainly diabetic, hypertensive, and vascular renal disease. The well-known example of polycystic kidney disease reminds us that the diagnosis of primary kidney disease may indeed play an important role for the interpretation of erythropoietin levels. In these patients, erythropoietin secretion is markedly preserved, despite advanced renal insufficiency, and some of these patients may even remain independent of erythropoietin while on dialysis [4]. Therefore, one should look closely at the main trigger of erythropoietin secretion in each of these diseases, namely, the partial pressure of oxygen in the renal medulla.

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